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10/575,474	04/12/2006	Hiroko Kojima	062405	3422

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,474	KOJIMA ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 08/019/2007 has been entered. Claims 9-12 are pending. Claims 1-8 and 13 were cancelled. Claims 9-12 were amended. Claims 9-12 are currently under examination.

This application 10/575,474 filed on 04/12/2006 is a 371 of PCT/JP04/15673 filed on 10/15/2004 and claims the priority of foreign application JAPAN 2003-355505 filed on 10/15/2003.

Claim Objections

1. Previous objection of claims 9-12 because of the following informalities: claim 9 recites the phrase "a gene *of* an osteo-/chondro-inducible transcription factor Cbfa1", which does not conform to the generally accepted scientific terms, is ***withdrawn*** because the claims have been amended. Specifically claim 9 now reads as follows: An implant consisting of a bioadaptable porous material on which an adenoviral or retroviral vector carrying a gene encoding an osteo-inducible transcription factor Cbfa1 is adsorbed.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Previous rejection of claim 9 under 35 U.S.C. 102(b) as being anticipated by Yang et al. (Yang et al., In vitro and in vivo synergistic interactions between the Runx2/Cbfa1 transcription factor and bone morphogenetic protein-2 in stimulating osteoblast differentiation. *J Bone Miner Res.* 18(4): 705-15, 2003), is ***withdrawn*** because claim 9 has been amended and Applicant's arguments filed 08/01/2007 have been fully considered and they are persuasive.

Specifically, Applicant argues that claim 9 is directed at an implant consisting of a bioadaptable porous material. The bioadaptable porous materials in the present invention act as a scaffold, which enables the sustained release of the Cbfa1 gene at the defective site. This results in remarkable osteogenesis (bone formation). On the other hand, Yang describes that interactions of various factors are needed for osteogenesis. Applicant also argues that, in Yang et al., cells transduced with AdCMV-Runx2 (an adenoviral vector carrying a gene encoding Cbfa1) strongly express osteoblast markers such as ALP, and the cells of Yang are subcutaneously implanted into immunodeficient mice. Applicant further argues that, in Yang, the cells transduced with AdCMV-Runx2 (Cbfa1) are implanted into mice without using a scaffold such as bioadaptable porous material.

In response, the Examiner notes that the specification discloses the following: In the present description, the term "porous" refers to a porosity of 30% or higher. The pore size of the bioadaptable materials according to the present invention is not particularly limited,

although a diameter of approximately 50 μm to 500 μm is preferable (See paragraph [0021], 2007/0031465). Therefore, the cells transduced with AdCMV-Runx2 (Cbfa1) implanted into mice are not encompassed by the amended phrase "a bioadaptable porous material" recited in claim 9.

3. Claims 9-12 remain rejected under 35 U.S.C. 102(e) and under 35 U.S.C. 102(a) as being anticipated by Kumta et al. (Kumta et al., U.S Patent application Publication 2003/0219466, Publication date, Nov. 27, 2003, filed on Mar. 19, 2003). Applicant's arguments filed 08/01/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 4-5 of the office action mailed on 05/04/2007.

For clarity and completeness of this office action, the rejection of record advanced on pages 4-5 of the office action mailed on 05/04/2007 is reiterated below with editorial corrections deleting statements that are only relevant to the canceled claim 13.

Kumta et al. teach nanocrystalline hydroxyapatite particles and a method for production of the nanocrystalline hydroxyapatite particles. The nanocrystalline hydroxyapatite particles find use in tissue engineering applications, for example bone and tooth engineering and repair applications (See abstract, Kumta et al., 2003).

With regard to an implant consisting of an bioadaptable material and its association with DNA (claims 9-12 of instant application), Kumta et al. teach polymer matrices of use as a tissue engineering substrate as described typically are "bioerodible," or "biodegradable," unless a permanent matrix is desirable. The terms "bioerodible," or "biodegradable," as used refer to materials, which are enzymatically or chemically degraded *in vivo* into simpler chemical

species. Either natural or synthetic polymers can be used to form the matrix, which can be implanted in vivo (See parag. [0118], column 12, Kumta et al., US 2003/0219466). And the *hydroxyapatite* prepared by the methods described herein, for example complexed with a biomaterial such as DNA, may be associated with any suitable matrix (See parag. [0053], column 5, Kumta et al., US 2003/0219466). Furthermore, Kumta et al. teach *adenoviral vector* mediated gene transfer (See parag. [0117], column 12; parag. [0044], column 4, Kumta et al., 2003), and expression of gene (See Kumta et al., parag. [0042], column 4, US 2003/o219466).

With regard to Cbfa1 (claim 9 of instant application), Kumta et al. teach in one embodiment, the biomaterial is DNA that contains a gene, such as a bone morphogenetic protein gene. Examples of suitable genes include rhBMP-2 and *Runx2*. At the time of filing of instant application, Runx2 is also known as Cbfa1 (core binding factor alpha 1) and Osf2 (osteoblast specific factor 2). For instance, Doll et al. (U.S. Patent Publication No: U.S. 2003/0235564, Publication date, Dec. 25. 2003) disclosed transcription factor Runx2, also referred to as Cbfa1 and as Osf2, which is a regulator of osteoblast differentiation (See parag. [0022], column 3, Doll et al. U.S. 2003/0235564).

With regard to β-TCP (β-tricalcium phosphate) (claims 10-12 of instant application), Kumta et al. teach the calcium deficient hydroxyapatite decompose into β-TCP and CaO accompanied by slight weight loss (See Kumta et al., parag. [0086], column 9, US 2003/0219466).

Thus, Kumta et al. clearly anticipates claims 9-12 of instant invention.

Applicant's arguments

With regard to whether Kumta et al. anticipates claims 9-12 of instant application, Applicant argues that Kumta does not *adsorb* the vector on a bioadaptable porous material. Rather, in Kumta, an adenoviral vector is conjugated in the hydroxyapatite nano particle. Thus, the present invention enables *in situ* sustained release of Cbfa1 gene and achieves remarkable bone regeneration. This is clearly demonstrated in the Examples of the present invention. Applicant argues that the conjugate of Kumta needs a large amount of adenoviral vector to synthesize the hydroxyapatite conjugate, because the adenoviral vector should be incorporated into the hydroxyapatite during the synthesis process of the hydroxyapatite conjugate. In contrast, the implant of the present invention is produced using a smaller amount of adenoviral vector via adsorption by the porous body. Applicant also argues that the bioadaptable porous material used in the present invention shows higher cell infiltration and angio-invasive properties, while the hydroxyapatite nano particle used in Kumta shows no such properties. Applicant further argues that there does not appear to be any suggestion or disclosure, by Kumta et al., of a β-TCP bioadaptable porous material comprising an adenovirus carrying a gene encoding Cbfa1.

Response to Applicant's arguments

Applicant's arguments filed 08/01/2007 have been fully considered and they are not persuasive. With regard to the meaning of the word "adsorb" recited in claim 9, the specification discloses the following in the context of incorporation of vectors into bioadaptable materials: *Vectors may be incorporated into bioadaptable materials via any technique without particular limitation*; however, it is preferable that vectors be incorporated as homogenously as possible. *Vectors may be chemically bound to the bioadaptable materials*, or they may be

merely physically adsorbed thereon. In the case of β-TCP, for example, the bioadaptable materials are soaked in a vector-containing solution (i.e., a medium) to allow β-TCP to homogenously adsorb vectors (See paragraph [0023], US 2007/0031465, publication of instant application). Therefore, the breadth of claims 9-12 of instant application, in light of specification, encompasses the adenoviral vector carrying a gene encoding Cbfa1, which is conjugated in the hydroxyapatite nano particle, as taught by Kumta et al. It is noted that the arguments on the claimed implant being more effective than that disclosed by Kumta et al. is irrelevant because they are disclosed in the specification, not recited in the claims of instant application. Furthermore, even if the intended use were recited in the claims, they bear limited, if any, patentable weight with regard to the implant (a product) currently under examination.

With regard to the argument whether the disclosure by Kumta et al. reads on β-TCP bioadaptable porous material comprising an adenovirus carrying a gene encoding Cbfa1, the Examiner notes that Kumta et al. clearly indicate the composition and chemical relationship of hydroxyapatite and β-TCP in the context of using these bioadaptable porous material for delivery of nucleic acid (See Kumta et al., Example 1, paragraphs [0053] and [0074] to [0094], US 2003/0219466).

4. Claims 9-12 remain rejected under 35 U.S.C. 102(e) and under 35 U.S.C. 102(a) as being anticipated by Doll et al. (Doll et al., U.S Patent application Publication 2003/0235564, Publication date, Dec. 25, 2003, filed on May 13, 2003). Applicant's arguments filed 08/01/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 5-7 of the office action mailed on 05/04/2007.

For clarity and completeness of this office action, the rejection of record advanced on pages 5-7 of the office action mailed on 05/04/2007 is reiterated below with editorial corrections deleting statements that are only relevant to the canceled claim 13.

Doll et al. teach a pharmaceutical composition comprising in combination the Runx2 protein, a polynucleotide encoding the Runx2 protein, or a cell that has been transformed with a polynucleotide encoding Runx2 protein, in a pharmaceutically acceptable carrier, the carrier comprising a bio-compatible, biodegradable polymeric matrix. Another aspect of the invention includes a device comprising the above-described pharmaceutical composition in combination with a sterile and substantially antigen-free, pre-shaped allograft or xenograft bone implant (See abstract, Doll et al., 2003).

With regard to an implant consisting of a bioadaptable material and its association with DNA (claims 9-12 of instant application), Doll et al. teach a method for repairing a bone defect comprising administering to a mammalian patient at the site in need of treatment a pharmaceutical composition, comprising in combination the Runx2 protein, a polynucleotide encoding the Runx2 protein, or a cell that has been transformed with *a polynucleotide encoding Runx2 protein*, in a pharmaceutically acceptable carrier wherein the carrier is a bio-compatible, biodegradable polymeric matrix (See abstract, Doll et al., 2003). Doll et al. teach viral vectors have higher transaction (ability to introduce genes) abilities than do most chemical or physical methods to introduce genes into cells. And the viral vectors include retroviral vectors and adenoviral vectors (See parag. [0096], [0097], and [0098], Doll et al., 2003).

With regard to Cbfa1 (claim 9 of instant application), Doll et al. teach transcription factor Runx2, also referred to as Cbfa1 (core binding factor alpha 1) and as Osf2 (osteoblast

specific factor 2), which is a regulator of osteoblast differentiation (See parag. [0022], column 3, Doll et al. 2003).

With regard to β-TCP (β-tricalcium phosphate) (claims 10-12 of instant application), Doll et al. teach the reports on the use of β-tricalcium phosphate for implantation; and reports on the use of demineralized bone implants (See parag. [0053], column 7, Doll et al., 2003).

Thus, Doll et al. clearly anticipates claims 9-12 of instant invention.

Applicant's arguments

With regard to whether Doll et al. anticipates claims 9-12 of instant application, Applicant argues that while Doll et al. describes the use of some elements of the invention, it does not disclose or suggest the specific constitution of the present invention. That is, Doll does not disclose or suggest "an implant consisting of a bioadaptable porous material on which an adenoviral or retroviral vector carrying a gene encoding an osteo- inducible transcription factor Cbfa1 is adsorbed." Doll does not disclose or suggest such an implant.

Response to Applicant's arguments

Applicant's arguments filed 08/01/2007 have been fully considered and they are not persuasive. With regard to the meaning of the word "adsorb" recited in claim 9, the specification discloses the following in the context of incorporation of vectors into bioadaptable materials: *Vectors may be incorporated into bioadaptable materials via any technique without particular limitation*; however, it is preferable that vectors be incorporated as homogenously as possible. *Vectors may be chemically bound to the bioadaptable materials*, or they may be merely physically adsorbed thereon. In the case of β-TCP, for example, the bioadaptable

materials are soaked in a vector-containing solution (i.e., a medium) to allow β-TCP to homogenously adsorb vectors (See paragraph [0023], US 2007/0031465, publication of instant application). Therefore, the breadth of claims 9-12 of instant application, in light of specification, encompasses a pharmaceutical composition, comprising in combination the Runx2 protein, a polynucleotide encoding the Runx2 protein (i.e. Cbfa1), or a cell that has been transformed with a polynucleotide encoding Runx2 protein, in a pharmaceutically acceptable carrier wherein the carrier is a bio-compatible, biodegradable polymeric matrix (See abstract, Doll et al., 2003), as taught by Doll et al. In other words, the pharmaceutical composition, including pharmaceutically acceptable carrier being a bio-compatible, biodegradable polymeric matrix, taught by Doll et al. reads on the limitation "an adenoviral or retroviral vector carrying a gene encoding an osteo-induvcible transcription factor Cbfa1 is absorbed" recited in claim 9.

With regard to the argument whether the disclosure by Doll et al. reads on β-TCP bioadaptable *porous* material comprising an adenovirus carrying a gene encoding Cbfa1, the Examiner notes that Doll et al. clearly indicate the use of β-tricalcium phosphate (β-TCP), a bio-compatible, biodegradable porous polymeric matrix, for implantation (See parag. [0053], column 7, Doll et al., 2003) in the context of a pharmaceutical composition, comprising in combination the Runx2 protein, a polynucleotide encoding the Runx2 protein (i.e. Cbfa1 recited in claim 9 of instant application), or a cell that has been transformed with a polynucleotide encoding Runx2 protein (i.e. Cbfa1), in a pharmaceutically acceptable carrier wherein the carrier is a bio-compatible, biodegradable polymeric matrix (See abstract, Doll et al., 2003).

It is noted that Doll et al. do not teach the verbatim of the claims recited in the instant application, which Applicant appears to argue as the requirement for the art to be anticipatory.

However, Doll et al. do teach each and every element of the claims 9-12 for the reasons of record advanced on pages 5-7 of the office action mailed on 05/04/2007, further discussed and reiterated above in this office action.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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